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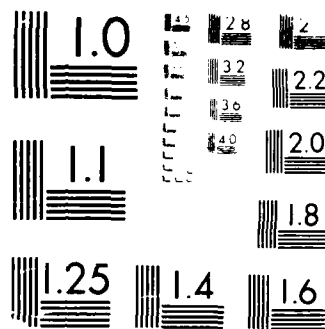
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DEVELOPMENT OF MICROCOMPUTER METHODS FOR
ANALYSIS AND SIMULATION OF CLINICAL
PHARMACOKINETIC DATA RELEVANT TO
NEW DRUG DEVELOPMENT

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ANNUAL REPORT

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Durham, North Carolina 27710

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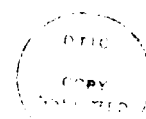
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The research proposed under this contract is a feasibility study in the development of applications of new microcomputer graphics technology to the continuing development of comprehensive programs for analysis, interpretation, and simulation of pharmacokinetic data, dose-response kinetic data, and other data relevant to new drug development, for use with the Tektronix 4052 Microcomputer Graphics System. The combination of such modern analytical and illustrative methods in clinical pharmacology, based on new high-speed microcomputers and associated graphics, are thought to greatly reduce both cost and		

time involved in the overall process of clinical evaluation of new drugs in the U.S. Army Drug Development Program.

The work performed during the past twelve months of the contract includes the following:

1. Continuing developments of the programs for the analysis and simulation of non-linear kinetic data.
2. Continuing development of a program package for clinical pharmacological problems.
3. Development of a translation program for the conversion of various sets of pharmacokinetic parameters into a uniform set.
4. Completion of a final report on bioavailability study on mefloquine.



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SUMMARY

The research proposed under this contract is a feasibility study in the development of applications of new microcomputer graphics technology to the analysis and interpretation of clinical pharmacological data. This involves continuing development of comprehensive programs for analysis, interpretation, and simulation of pharmacokinetic data, dose-response kinetic data, and other data relevant to new drug development, for use with the Tektronix 4052 Microcomputer Graphics System. The combination of such modern analytical and illustrative methods in clinical pharmacology, based on new high-speed microcomputers and associated graphics, are thought to greatly reduce both cost and time involved in the overall process of clinical evaluation of new drugs in the U.S. Army Drug Development Program.

The work performed during the past twelve months of the contract includes the following:

1. Improvements in the programs for analysis and simulation of non-linear pharmacokinetic data. In order to simplify the use of these programs, a menu of commonly used kinetic models has been added, allowing the user to select a pre-written set of differential equations instead of having to type in a description of the model. This modification significantly reduces the level of pharmacokinetic knowledge needed to successfully use these programs. Additionally, this menu has been structured so as to be easily modified and extended, so that further models can be added to the existing set, allowing the programs to be customized for use in any specific case.

2. Further development of programs for statistical analysis of clinical pharmacologic data. A number of modifications have been made to the programs for the various nonparametric statistical tests, providing the user with better facilities for reviewing and correcting the data they have entered, as well as making the programs more consistent in the presentation of results. We have also continued work on the parametric analysis of variance programs for multiple comparisons and for cross-over design experiments, adding some new capabilities for complex hypothesis testing.

3. Development of a translation program for the conversion of various sets of pharmacokinetic parameters into a uniform format. This program is designed to allow the use of published pharmacokinetic data for comparison with the results of our data fitting package or for use with our kinetic simulation program. Since published studies frequently express the results of their analysis in terms of a particular model, it is necessary to calculate the equivalent set of model-independent parameters before making use of the data. The program has been designed to allow the translation of descriptions of one- or two-compartment systems into the format used by our linear pharmacokinetic programs. In addition to this function, it also performs the necessary unit conversions so that all the half-life figures, for example, can be expressed in terms of the same time scale.

4. Design of drug dosage regimens. Development was initiated towards a program which could help design optimal drug dosage regimens using an algorithm involving pharmacokinetic and pharmacodynamic data. However, due to lack of illustrative data in the literature and slow progress of needed theoretical work, the development of this program was not pursued further at this point.

5. Completion of the final report on a bioavailability study comparing two tablet formulations of mefloquine. This project was begun in the previous contract year and was partially described in our fourth annual report. Some additional analysis was done this year, and the entire results are contained in our final report on this study.

An additional goal described in our renewal proposal last year was the development of a dose-response analysis program for use with the Radio Shack TRS-80 computer. This was intended to allow the use of a less expensive computer than the Tektronix 4052 for the analysis of concentration-effect data. At the time of this proposal, a TRS-80 was easily accessible nearby, and we had planned to use it for development of this program. Unfortunately, this machine became unavailable for our use, leaving no means for working on this project without buying a TRS-80. We did not feel that such a purchase would have been justified for the development of only one program, so work was stopped at this particular point.

BACKGROUND

The process of drug development has been both complicated and facilitated by the trend toward early application of the methods of clinical pharmacokinetics. Current practice and existing and proposed new Food and Drug Administration Regulations demand sophisticated evaluation of drug bioavailability and descriptive pharmacokinetics in Phase I clinical studies. This requires development of assay methods for new drugs and their metabolites and methods for evaluation of concentration vs time data to obtain relevant parameters to characterize drug behavior. Of similar importance is knowledge of characteristics of relationships between dose or concentrations and pharmacological response. The information thus obtained from pharmacokinetic and pharmacodynamic studies relates directly to the optimal design of dosing schedules of new drugs in man, including individualization of therapy due to disease processes or other factors which may affect drug behavior. In this regard the eventual course of development through Phase II and Phase III clinical studies is rendered less empirical and ultimately more efficient in both time and cost, by minimizing the use of scarce resources.

Modern computer technology has greatly enhanced the capability of these methods and made possible their applications to clinical pharmacokinetics. A number of available computer programs have been frequently employed for this purpose. Those which have been developed for use specifically in clinical pharmacokinetics are based on compartmental methods of analysis and yield estimates of parameters associated with preselected compartmental models. While useful and informative, they lack the ease of use and cognitive appeal of direct graphic simulations and graphics-assisted data analysis. It is in the interest of developing general purpose programs with the advantages of computer graphics that the present contract was initially pursued.

Previous experience with the Tektronix 4051 and 4052 Microcomputer Graphics Systems indicated that this was an especially suitable microcomputer system for our purposes. While similar systems are now available from a variety of sources, it is in the interest of conformity with existing systems in the U.S. Army Drug Development Program at the Walter Reed Army Institute of Research that the Tektronix System has been employed. The present Tektronix 4052 System in our laboratory and for which the programs to be described were developed is identical to that now in use at Walter Reed. A data communications interface has been installed to facilitate direct transmission of programs and data between these two facilities.

PROCESS

A. Programs for Analysis and Simulation of Pharmacokinetic Data in Non-linear Kinetic Systems.

The program package for pharmacokinetic analysis of data from non-linear systems and the simulation program which accompanies it have undergone some simplifications during the past year. In the original versions of these programs, the user had to enter the differential equations describing the model into the program, requiring a sophisticated level of knowledge of pharmacokinetics and of differential equations. We felt that this put an unnecessary burden on the user of the programs, and have now modified them to allow a menu of choices to be presented so that a previously written model can be automatically re-loaded. This feature takes advantage of the ability of Tektronix Basic to load code from a file into an executing program, using the APPEND statement. The nature of this operation makes it very easy to add to the menu of models by adding further files containing the necessary differential equations, and then editing the menu to reflect the additional choices available. Presently, the options available in the standard menu of models include one-compartmental models with Michaelis-Menten type elimination, with input from IV bolus, IV infusion, or oral first-order absorption. These models are useful themselves, and can also serve as a template for the development of further, more complex systems of differential equations for these programs.

B. Statistical Program Package for Analysis of Clinical Pharmacologic Data.

These programs have had a number of various small changes made this year. In the set of non-parametric tests which are available, the portions of the programs dealing with the entry and correction of data have been rewritten to make them easier to use, as well as making all of the programs more consistent in their interactions with the user. Now, all of the programs allow data to be listed on the screen for review before any results are printed, with options available for changing data values and for deletion of incorrect points as well as entry of additional points. Further changes have been made to more clearly identify the groups of data that are printed out with the results of the statistical analysis. Because the same kinds of changes have been made in all of these programs at the same time, the user can now deal with each of the programs in the same fashion, making them all easier to use. Work has also been done on the parametric analysis of variance programs to allow specification of whether all possible comparisons between groups should be performed, or whether specific combinations should be used. In addition, the multiple comparison method developed by Scheffe, which is based on use of the Chi-square probability function, has been added. This procedure, like the Bonferroni tests which were already available in this program, can be computed directly without requiring the use of tables of critical values. We have been unable to find similar direct methods to use with the methods of Duncan or of Dunnett. Because of this lack, these procedures are still not available as an automatic component of the program, although the user can easily complete either of these tests using the program output together with a table from any of several standard references.

C. Translation Program for Converting Different Groups of Pharmacokinetic Parameters into Model-independent Format.

This program is designed to help convert pharmacokinetic data, which is often presented in incompatible formats, into a standard form based on the model-independent representation used in our data fitting program package. This parameter translation is useful for a number of different purposes. It allows direct comparison of data about the same drug from many different sources, including the output of our own analysis package. It also makes it possible to convert published results into the format needed for use of our pharmacokinetic simulation program, allowing examination of the results of various dosing regimens based on data from other investigators. These types of applications can result in a saving of time and money, since experiments need not be duplicated simply to obtain data in a different format. The program is capable of converting data representing a one- or two-compartment pharmacokinetic model with input through injection, infusion, or oral administration into a single standard format, using the sum-of-exponential-terms representation. The input to the program may be expressed in terms of volumes of distribution, half-lives, time of peak concentration, clearance, rate constants of absorption or elimination, or concentration at time of injection or maximal absorption. If requested, the program can perform unit conversions on some of the input parameters to make them consistent, for example if volume is expressed in liters and half-life in hours, but clearance is in ml/min. This feature can help to reduce confusion when comparing data from different sources.

D. Design of Drug Dosage Regimens.

While the programs developed under this contract are useful for the analysis and simulation of pharmacokinetic and pharmacodynamic data, they have not been designed to address directly the optimal design of drug dosage regimen. We had therefore proposed to develop an algorithm for helping with the design of optimal dosage regimens when both pharmacokinetic and pharmacodynamic data are available. Initial theoretical work, outlined in our last renewal proposal, indicated the feasibility of such an algorithm. It was clear from the beginning that such a program would require good useful published data to illustrate the usefulness and meaningfulness of such a program. However, as we were unable to identify a suitable data set and further theoretical development in this area, which now become more pressing to counteract the lack of data, was slower than anticipated, it was decided not to pursue this project at this particular point.

E. Special Data Analysis Projects.

A request was received last year from LTC Charles Pamplin, asking us to perform an analysis of data from a study comparing the bioavailability of two different tablet formulations of mefloquine. A description of our method of analysis was included in last year's annual report, but the final report concerning our conclusions was not available for inclusion at that time. Since then, some further tests have been made on the data, all confirming our earlier results with regard to the quicker absorption and higher availability of the Hoffman-LaRoche preparation. A detailed report on these tests, containing all of the results from our analysis, was completed and submitted to LTC Pamplin last spring.

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